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CHEMICAL KINETICS ON SURFACES: A SINGULAR LIMIT OF A REACTION-DIFFUSION SYSTEM*

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Abstract. We show that chemical kinetics relations can be used to describe processes that involve binding and dissociation reactions that take place on surfaces. From a mathematical perspective, the problem we study is a singular limit of a reaction-diffusion system in which one of the variables concentrates on a lower-dimensional set in the limit, while the other continues to diffuse in a fixed domain.

Key words. chemical kinetics, surface, binding, dissociation, singular limit, invariant region

AMS subject classifications. 92C45, 92C50, 35K57, 35B25

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1. Introduction.

Numerous biological processes involve binding and dissociation reactions that take place on surfaces. For example, in *antibody-antigen* interactions, antibodies immobilize and agglutinate infectious agents by binding to specific receptors located on the surface of antigens [1, 19, 22]. Additional examples include the binding of proteins to cell membranes either to initiate transduction of external signals into the cell (*signal transduction*) or to open the ion channels of the membrane (see, e.g., [18]); the binding of microbiological cultures to attachment sites on the inner walls of flow reactors [12]; and the phenomenon of surface plasmon resonance, which involves interactions of biopolymers with various ligands [13].

A natural way to model surface reactions is to adapt the standard chemical-kinetics approach used for reactions occurring in volumes. This means that the binding rate for surface reactions is assumed to be proportional to the product of the volumetric concentration of the reactant at the surface and the surface concentration of the binding sites [18, 20]. There is a methodological problem with this approach, however, since chemical-kinetics relations are usually derived under the assumption that reactions take place in a volume, in which the two reactants are well mixed.

Our goal here is to justify the use of chemical-kinetics relations for reactions that take place on surfaces. To do so, we will first construct a volumetric model in which the binding sites, and hence also the binding and dissociation reactions, take place in a narrow volumetric layer around the surface. We will then show that as the width of the binding sites layer shrinks to zero, the volumetric model reduces to a surface model, in which binding sites are located on the surface, and for which the reactions are still described by chemical-kinetics relations.

From a mathematical perspective, the problem we study is a singular limit of a

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reaction-diffusion system. The problem here differs from the widely studied case of thin domains (see, e.g., [10]) in that here only one of the variables concentrates on a lower-dimensional set in the limit, while the other continues to diffuse in a fixed domain.

In this study we analyze the problem of chemical kinetics on surfaces in the context of a mathematical model for a novel in-vivo imaging technique for identifying and locating cancerous tumors, which are sphere-like, isolated, three-dimensional objects, with a smooth boundary.[1] This model consists of a diffusion equation in the volume surrounding the tumor, and binding and dissociation reactions that take place on the tumor surface. We note, however, that the methodology developed in this study, namely, the study of "surface models" as the limit of "volumetric models," can be applied to other models that involve binding and dissociation reactions on surfaces. Moreover, our approach may also be relevant to problems in combustion (e.g., burning of coal) in which the reactions take place between one or more species (e.g., coal) that are confined to narrow regions near the reactor boundaries and other species that are free to diffuse over larger domains (e.g., oxygen) [2].

The paper is organized as follows. In section 2 we construct two mathematical models, a surface model and a volumetric model. In section 3 we present a heuristic derivation of the surface model from the volumetric model. This is done by taking the limit as the width of the volumetric layer tends to zero while assuming that the limits of the concentrations exist in appropriate senses. For further clarity, we consider only the radially symmetric case. In section 4 we rigorously prove that solutions of the volumetric model converge to those of the surface model, without assuming radial symmetry. Finally, in section 5 we comment briefly on the possibility of extending our results to other models.

2. Mathematical models.

2.1. Fluorophore-antibody imaging. Our interest in this problem originated from the need to model a novel in-vivo imaging technique for identifying and locating cancerous tumors [11]. This method is based on one of the immune system responses to tumors, which is the concentration of white blood cells, known as T cells, around the tumor. These T cells have receptors which are specific to some antibodies of the immune system. The imaging technique involves selecting an antibody with high specificity to T cells [3], artificially conjugating it with a fluorescent marker compound, and injecting the fluorescenated antibodies into the suspected tumor area [5, 6, 7, 8, 9]. After some time, the fluorescenated antibodies, hereinafter denoted *markers*, will diffuse away from the tumor area, except for those that are bound to the T cell receptors around the tumor. Hence, when an external laser excitation is applied, the fluorescence of the markers indicates the location of the tumor.

The mathematical model that we use to describe the method of fluorophore-antibody imaging involves diffusion of markers in the tissue, binding of markers to T cells receptors (binding sites), and dissociation of markers that are already bound to sites. The methodology developed in this study can, however, be extended to more complex models that allow for diffusion of markers into the tissue area, advection effects, etc.

To simplify the presentation, in this section we assume that the tumor is the radially symmetric ball $0 \le r < r_{tumor}$, where r is the radial distance from the tumor

[1] This corresponds to the common solid tumors such as breast, lung, and sarcoma, at the early stages of the tumor (i.e., before it develops a nonsmooth surface).

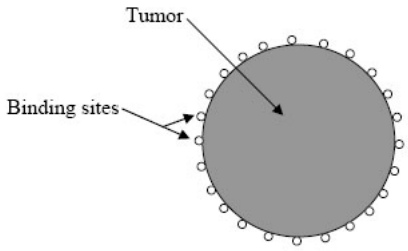

FIG. 1. *The surface model. Binding sites are located on the boundary of the tumor.*

center. The assumption of radial symmetry is reasonable for young, small-size tumors. Our results, however,are also valid for more advanced tumors, which are half-spheres or isolated, three-dimensional lumps, so long that their boundary remains smooth (see section 4). For simplicity we also assume that the initial markers distribution is radially symmetric.

2.2. The surface model. We first develop a surface model in which the T cell binding sites are located on the tumor surface (see Figure 1). In the tissue area, the motion of the markers is governed by the diffusion equation

$$\frac{\partial M(r,t)}{\partial t} = D\Delta M(r,t), \qquad 0 < t, \quad r_{tumor} < r < \infty, \tag{1}$$

where $M(r,t)$ is the volumetric concentration of the free (i.e., unbound) markers, and D is the diffusion coefficient of markers in the tissue. The initial condition for (1) is

$$M(r,0) = M_0(r), \tag{2}$$

where $M_0(r)$ is the initial concentration of markers.

Let us assume that chemical-kinetics relations can be used to model the reactions that take place on a surface. Then the free sites concentration at the tumor surface ($r = r_{tumor}$) is governed by the equation

$$\frac{\partial S(t)}{\partial t} = k_d^{sur}[S_{tot} - S(t)] - k_b^{sur} M(r_{tumor}, t) S(t), \tag{3}$$

where $S(t)$ denotes the free sites concentration, k_b^{sur} and k_d^{sur} are the binding and dissociation rate constants, respectively, and S_{tot} is the total concentration of sites, both free and occupied. Equation (3) shows that the free sites concentration increases as a result of dissociation of marker-site complexes and decreases as a result of binding of free markers to binding sites. The dissociation rate is linearly proportional to the bound sites concentration, $[S_{tot} - S(t)]$. Under the assumption of chemical kinetics, the binding rate is linearly proportional to the concentration of free binding sites, $S(t)$, and also linearly proportional to the concentration of free markers on the tumor boundary, $M(r_{tumor}, t)$.

We assume that before the injection of markers (i.e., at $t = 0$), all binding sites are unoccupied, so the initial condition for the sites equation is given by the total sites concentration S_{tot}, i.e.,

$$S(0) = S_{tot}. \tag{4}$$

We now derive the boundary conditions for the markers at the tumor boundary. Markers may be either free (i.e., in the tissue area) or bound (to T cell binding sites). If we assume that a single marker binds to a single site, then the concentration of bound markers on the surface equals $S_{tot} - S(t)$. In view of the fact that the total area of the tumor surface is $4\pi r_{tumor}^2$, the total number of bound markers is then $4\pi r_{tumor}^2 [S_{tot} - S(t)]$. Thus, the global conservation of markers is given by

$$\underset{\text{bound markers}}{4\pi r_{tumor}^2 [S_{tot} - S(t)]} + \underset{\text{free markers}}{4\pi \int_{r_{tumor}}^{\infty} M(r,t)\, r^2 dr} = \underset{\text{total markers}}{4\pi \int_{r_{tumor}}^{\infty} M_0(r)\, r^2 dr}.$$

Differentiating this equation with respect to t, and using (1) and the formula for Δ in polar coordinates, shows that

$$\begin{aligned} r_{tumor}^2 \frac{\partial S(t)}{\partial t} &= \int_{r_{tumor}}^{\infty} \frac{\partial M(r,t)}{\partial t}\, r^2 dr \\ &= D \int_{r_{tumor}}^{\infty} \Delta M(r,t)\, r^2 dr = D \int_{r_{tumor}}^{\infty} \left[\frac{\partial^2 M}{\partial r^2} + \frac{2}{r} \frac{\partial M}{\partial r} \right] r^2 dr \\ &= D \int_{r_{tumor}}^{\infty} \frac{\partial \left[r^2 \frac{\partial M}{\partial r} \right]}{\partial r} dr = -D r_{tumor}^2 \frac{\partial M}{\partial r}(r_{tumor}, t), \end{aligned} \tag{5}$$

provided that the concentration of markers decays sufficiently rapidly at large distances so that they have no flux at infinity. Upon substituting in the value of $\frac{\partial S(t)}{\partial t}$ from (3) we find that the boundary condition at the tumor surface is given by

$$\frac{\partial M}{\partial r}(r_{tumor}, t) = \frac{1}{D} \{ k_b^{sur} M(r_{tumor}, t) S(t) - k_d^{sur} [S_{tot} - S(t)] \}. \tag{6}$$

2.3. The volumetric model. As mentioned in the introduction, there is a methodological problem with the surface model since we used chemical-kinetics relations to model surface reactions; see (3). In order to avoid this problem, we now adopt a different approach and assume that the T cell binding sites are located in a narrow volumetric layer around the tumor (see Figure 2). This approach also has a physiological justification. Indeed, data collected in histological staining experiments show that T cells are not located strictly on the tumor surface but rather in a thin volumetric layer around the tumor (see Figure 3). The existence of a layer of T-lymphocytes (CD3 positive cells) around the tumor was also reported in, e.g., [4, 25].

Let ε denote the width of the volumetric layer in which binding sites are located. Then the volume density $S_{\text{tot}}^{\varepsilon}(r)$ of total binding sites vanishes identically for $r > r_{tumor} + \varepsilon$, i.e.,

$$S_{\text{tot}}^{\varepsilon}(r) \equiv 0 \qquad \text{for } r > r_{tumor} + \varepsilon. \tag{7}$$

Of course this implies that the density $S^{\varepsilon}(t,r)$ of free binding sites also vanishes for $r > r_{tumor} + \varepsilon$.

The equation of evolution for the concentration $M^{\varepsilon}(t,r)$ of free markers now takes the form

$$\begin{aligned} \frac{\partial M^{\varepsilon}(r,t)}{\partial t} &= D \Delta M^{\varepsilon}(r,t) + k_d^{vol} [S_{\text{tot}}^{\varepsilon}(r) - S^{\varepsilon}(r,t)] - k_b^{vol} M^{\varepsilon}(r,t) S^{\varepsilon}(r,t), \\ & 0 < t, \quad r_{tumor} < r < \infty, \end{aligned} \tag{8}$$

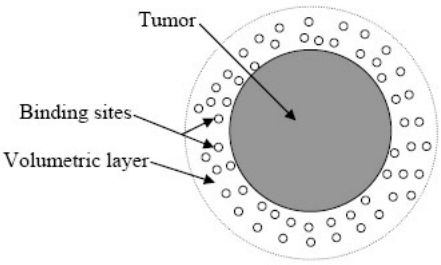

FIG. 2. *The volumetric model. Binding sites are located in a thin volumetric layer around the tumor.*

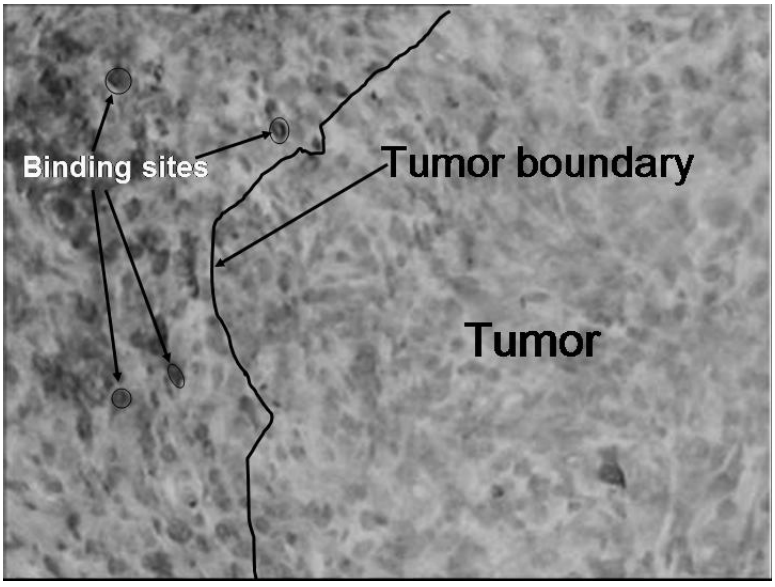

FIG. 3. *Histological staining of a 5-day old tumor squamous cell carcinoma in the oral cavity (mag. X200). Binding sites (stained in black) can be seen to the left of the solid line. Figure supplied by Dr. Gallya Gannot, National Institutes of Health, Bethesda, MD.*

where k_b^{vol} and k_d^{vol} are the volumetric model binding and dissociation rate constants, respectively. The first term on the right is the diffusion term, the second term describes the dissociation of marker-site complexes, and the third term describes the creation of these complexes. Note that in contrast to (3), there is no problem with using chemical-kinetics relations.

The rate of change of the free sites concentration is derived using chemical-kinetics relations, as was done for (3) of the surface model, yielding

$$\frac{\partial S^{\varepsilon}(r,t)}{\partial t} = k_d^{vol}\left[S_{\text{tot}}^{\varepsilon}(r) - S^{\varepsilon}(r,t)\right] - k_b^{vol} M^{\varepsilon}(r,t) S^{\varepsilon}(r,t). \tag{9}$$

The only difference is that now these reactions take place in a volumetric layer rather than on a surface as in the previous model.

As in the surface model, we assume that at time $t = 0$ all the binding sites are unoccupied. Therefore, the initial condition for the free sites concentration is given

by

$$S^\varepsilon(r,0) = S^\varepsilon_{\text{tot}}(r). \tag{10}$$

The initial distribution of markers will be assumed to be the same as for the surface model:

$$M^\varepsilon(r,0) = M_0(r), \tag{11}$$

independently of ε. We also assume that markers cannot diffuse into the tumor. Therefore, at the tumor surface we impose the no-flux boundary condition

$$\frac{\partial M^\varepsilon(r,t)}{\partial r}(r_{tumor},t) = 0. \tag{12}$$

3. Heuristic justification of the surface model from the volumetric model. We now show, under some scientifically natural assumptions, that as the width ε of the binding sites layer goes to zero the volumetric model reduces to the surface model.

As already mentioned, we assume that both models have the same initial distribution of markers, and that in both models all the sites are unoccupied at time $t = 0$. We also assume that both models have the same total number of sites, i.e.,

$$\underbrace{4\pi \int_{r_{tumor}}^{\infty} S^\varepsilon_{\text{tot}}(r)\, r^2\, dr}_{\substack{\text{total number of sites} \\ \text{for the volumetric model}}} = \underbrace{4\pi r^2_{tumor} S_{tot}}_{\substack{\text{total number of sites} \\ \text{for the surface model}}}. \tag{13}$$

Next, we assume that the solution $M^\varepsilon(r,t)$, $S^\varepsilon(r,t)$ of the volumetric model (7)–(12) and the solution $M(r,t)$, $S(t)$ of the surface model (1)–(4), (6) exist for all positive time and are unique.

Finally, we assume that as ε tends to zero both the concentration $M^\varepsilon(r,t)$ of markers in the volumetric model and the radial integral of the concentration $S^\varepsilon(r,t)$ of free sites in that model tend to definite values. In other words, we assume that

$$M^0(r,t) := \lim_{\varepsilon\to 0} M^\varepsilon(r,t) \quad \text{and} \quad \mathcal{S}^0(t) := \frac{1}{r^2_{tumor}} \lim_{\varepsilon\to 0} \int_{r_{tumor}}^{\infty} S^\varepsilon(r,t)\, r^2\, dr \tag{14}$$

exist. Furthermore, we assume that in the region $r > r_{tumor}$ those equations may be differentiated and integrated as often as needed, and that the order of the resulting derivatives, integrals, and limits may be freely interchanged.

PROPOSITION 3.1. *Under the above assumptions, the limits* (14) *of the volumetric model are the solution of the surface model with the same binding and dissociation constants. In other words,*

$$M^0(r,t) \equiv M(r,t), \tag{15}$$

and

$$\mathcal{S}^0(t) \equiv S(t), \tag{16}$$

the latter of which may also be expressed as

$$\lim_{\varepsilon\to 0} S^\varepsilon(r,t) \equiv S(t)\cdot\delta(r - r_{tumor}),$$

where δ is the Dirac δ function.

Proof. Since $S^{\varepsilon}_{\text{tot}}(r)$ is nonnegative, (7) plus (13) implies that

$$\lim_{\varepsilon\to 0} S^{\varepsilon}_{\text{tot}}(r) = S_{tot}\cdot\delta(r - r_{tumor}). \tag{17}$$

Similarly, since

$$0 \le S^{\varepsilon}(r,t\,) \le S^{\varepsilon}_{\text{tot}}(r), \tag{18}$$

it follows from (7) plus (14) that

$$\lim_{\varepsilon\to 0} S^{\varepsilon}(r,t) = \mathcal{S}^0(t)\cdot\delta(r - r_{tumor}), \tag{19}$$

and (17)–(19) imply further that

$$0 \le \mathcal{S}^0(t) \le S_{tot}.$$

We now show that for $r > r_{tumor}$ and $t \ge 0$, (15)–(16) hold, by showing that M^0 and $\mathcal{S}^0$ satisfy the surface model equations (1)–(4), (6).

Integrating both sides of (9) and taking the limit as $\varepsilon \to 0$ gives

$$\begin{aligned}
&\frac{1}{r^2_{tumor}}\lim_{\varepsilon\to 0}\int_{r_{tumor}}^{\infty}\frac{\partial S^{\varepsilon}(r,t)}{\partial t}\; r^2\,dr\\
&= \frac{1}{r^2_{tumor}}\lim_{\varepsilon\to 0}\int_{r_{tumor}}^{\infty} k_d^{vol}\left[S^{\varepsilon}_{\text{tot}}(r) - S^{\varepsilon}(r,t)\right]\; r^2\,dr\\
&\quad -\frac{1}{r^2_{tumor}}\lim_{\varepsilon\to 0}\int_{r_{tumor}}^{\infty} k_b^{vol} M^{\varepsilon}(r,t)S^{\varepsilon}(r,t)\; r^2\,dr.
\end{aligned}$$

Combining the above with (14), (17), and (19) gives

$$\mathcal{S}^0_t = k_d^{vol}\left[S_{tot} - \mathcal{S}^0\right] - k_b^{vol} M^0(r_{tumor},t)\mathcal{S}^0, \tag{20}$$

which corresponds to (3).

Similarly, in light of (14), (17), and (19) the limit $\varepsilon \to 0$ of the volumetric markers equation (8) yields

$$\frac{\partial M^0(r,t)}{\partial t} = D\Delta M^0(r,t) \qquad \text{for } r > r_{tumor}, \tag{21}$$

which is the analogue of (1).

From (10), (13), and (14) it follows that

$$\mathcal{S}^0(0) = S_{tot}.$$

More simply, (11) plus (14) implies

$$M^0(r,0) = M_0(r).$$

These two equations correspond to (4) and (2).

Finally, we derive the boundary condition for M^0 at $r = r_{tumor}$. In contrast to the assumed differentiability of the limits (14) for $r > r_{tumor}$, on the boundary we must expect that

$$\frac{\partial M^0}{\partial r}\Big|_{r_{tumor}} \ne \lim_{\varepsilon\to 0}\frac{\partial M^{\varepsilon}}{\partial r}\Big|_{r_{tumor}} = 0.$$

Indeed, although we assume, as in the surface model, that the markers cannot diffuse into the tumor, the existence of binding sites on the boundary effectively results in "disappearance" of markers at $r = r_{tumor}$. Hence, in the surface model the boundary $r = r_{tumor}$ is absorbing.

To derive the correct boundary condition there, we first note that the conservation law for the total number of markers may be written as

$$\frac{d}{dt}\frac{1}{r_{tumor}^2}\int_{r_{tumor}}^{\infty}\{M^\varepsilon(r,t)+[S^\varepsilon_{\rm tot}(r)-S^\varepsilon(r,t)]\}\ r^2\,dr=0,$$

since $M^\varepsilon(r,t)$ and $[S^\varepsilon_{\rm tot}(r)-S^\varepsilon(r,t)]$ are the concentrations of free and bound markers, respectively. Taking the limit as $\varepsilon\to 0$ and using (14), (17), and (19) gives

$$\frac{d}{dt}\left\{\frac{1}{r_{tumor}^2}\int_{r_{tumor}}^{\infty}M^0(r,t)\ r^2\,dr+\left[S_{tot}-\mathcal{S}^0\right]\right\}=0.$$

Therefore, by (14), (21), (20), and a calculation similar to (5) we get

$$\begin{aligned}\frac{\partial M^0(r_{tumor},t)}{\partial r}&=-\frac{1}{D}\frac{\partial \mathcal{S}^0}{\partial t}\\&=-\frac{1}{D}k_d^{vol}\left[S_{tot}-S^0(r,t)\right]+\frac{1}{D}k_b^{vol}M^0(r_{tumor},t)S^0(r,t),\end{aligned}$$

in accordance with (6). ∎

4. Rigorous justification of the surface model from the volumetric model. We now present a rigorous derivation of the surface model as the limit of the volumetric model. Unlike in sections 2 and 3, we do not make the assumption of radial symmetry.

4.1. Equations and results. When radial symmetry is not assumed we may write the equations governing the concentrations of unbound markers M^ε and unoccupied sites S^ε in the volumetric model in the form

$$M^\varepsilon_t(t,x)=D\Delta M^\varepsilon+k_d\,(S^\varepsilon_{\rm tot}(x)-S^\varepsilon)-k_bS^\varepsilon M^\varepsilon, \tag{22}$$

$$S^\varepsilon_t(t,x)=k_d\,(S^\varepsilon_{\rm tot}(x)-S^\varepsilon)-k_bS^\varepsilon M^\varepsilon. \tag{23}$$

Here x is a vector in $\mathbb{R}^d$ for some $d>1$ and $S^\varepsilon_{\rm tot}(x)$ is the total concentration of sites, which depends only on x since the sites are still assumed to remain stationary. Equations (22)–(23) are to hold in a smooth domain Ω in $\mathbb{R}^d$ whose inner surface $\partial_i\Omega$ is the boundary of the region occupied by the tumor. In order to reduce the technical complications we will assume that Ω is bounded, and its outer boundary, far from the tumor, will be denoted $\partial_o\Omega$. See Figure 4. However, the case when Ω is the entire exterior of the tumor surface $\partial_i\Omega$ could also be treated; in particular, the theorem on invariant regions (Theorem 3 below) is still valid in that case.

The total concentration of sites is clearly nonnegative, i.e.,

$$S^\varepsilon_{\rm tot}(x)\ge 0. \tag{24}$$

Also, since the sites are located near the surface of the tumor,

$$S^\varepsilon_{\rm tot}(x)=0\quad \text{for } d(x,\partial_i\Omega)>\varepsilon, \tag{25}$$

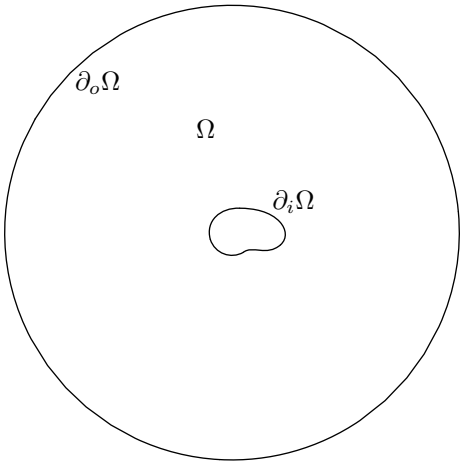

FIG. 4. *The domain Ω and its inner and outer boundaries $\partial_i\Omega$ and $\partial_o\Omega$.*

where $d(x, \partial_i\Omega)$ is the distance from a point x to the interior region Ω_i occupied by the tumor. We shall also assume that

$$S^{\varepsilon,0}_{\text{tot}}(y) := \int_0^\varepsilon S^\varepsilon_{\text{tot}}(y + \tau\nu)\, d\tau \text{ converges uniformly to some } S^0_{\text{tot}}(y) \text{ as } \varepsilon \to 0, \tag{26}$$

where ν denotes the unit normal on $\partial_i\Omega$ pointing into Ω. Note that conditions (24)–(26) are satisfied when $S^\varepsilon_{\text{tot}}(y + \tau\nu) = \frac{1}{\varepsilon}\phi(y)\psi(\frac{\tau}{\varepsilon})$, where ϕ and ψ are nonnegative continuous functions and $\psi(s)$ vanishes for $s > 1$.

The boundary condition for M^ε is

$$\nu \cdot \nabla M^\varepsilon = 0 \qquad \text{on } \partial\Omega, \tag{27}$$

which means that markers do not leave the region Ω. The initial conditions are

$$S^\varepsilon(0, x) = S^\varepsilon_{\text{tot}}(x), \tag{28}$$

which means that all sites are originally unoccupied, and

$$M^\varepsilon(0, x) = M_0(x) \geq 0. \tag{29}$$

Furthermore, we will assume that

$$S^\varepsilon_{\text{tot}}(x) M_0(x) \equiv 0, \tag{30}$$

i.e., that initial locations of the markers and sites do not overlap. Physically this is another expression of the assumption that time zero occurs before the sites start to become occupied, since if the marker and site locations overlapped at time zero, then some sites would have become occupied before then. Mathematically it avoids having an initial layer in which the site-occupation reaction would quickly reduce the size of the reaction term down to order one.

The local-in-time existence of a unique solution to (22)–(23), (27)–(29) can be obtained via the method of [23], by substituting the Green's function for the Neumann boundary value problem for $u_t = D\Delta u$ in place of the whole-space Green's function

in [23, eq. (2.7)]. Furthermore, the uniform bounds on the solution obtained in the next subsection imply that solution exists for all positive time.

The equations for the surface model are

$$M_t = D\Delta M \tag{31}$$

in Ω,

$$\nu \cdot \nabla M = \frac{k_d \left(S^0_{\rm tot}(x) - S\right) - k_b S M}{D} \tag{32}$$

on the inner boundary $\partial_i\Omega$ bounding the tumor region, (27) on the outer boundary $\partial_o\Omega$, and

$$S_t = k_d \left(S^0_{\rm tot}(y) - S\right) - k_b S M \tag{33}$$

on the inner boundary $\partial_i\Omega$. Although the existence of solutions to the surface model could be obtained by an appropriate adaptation of the method used for the volumetric model, we will obtain existence here as a by-product of our convergence result.

Our main result is that solutions of the volumetric model converge to those of the boundary model as the parameter ε tends to zero.

THEOREM 1. *Assume that S^ε_{tot} satisfies* (24)–(26). *Let $(M^\varepsilon, S^\varepsilon)$ be the solution of* (22)–(23) *and* (27) *having initial data of the form* (28)–(29) *belonging to $C^2(\overline{\Omega})$ and satisfying* (30). *Then as $\varepsilon \to 0$, M^ε and*

$$\mathcal{S}^\varepsilon(y,t) := \int_0^\varepsilon S^\varepsilon(y + \tau\nu, t)\, d\tau \tag{34}$$

converge to the unique solution (M, S) of (31) *and* (33) *satisfying* (32) *on $\partial_i\Omega$ and* (27) *on $\partial_o\Omega$ and having initial data* (29) *and $S(0,y) = S^0_{tot}(y)$.*

In the next subsection we will prove some uniform bounds that will be used in the subsequent subsection to take the limit as $\varepsilon \to 0$. Those uniform bounds also imply an upper bound for the fraction of sites that are occupied at any time.

THEOREM 2. *The ratio*

$$\frac{\int_\Omega \left[S^\varepsilon_{tot}(x) - S^\varepsilon(x,t)\right]\, dx}{\int_\Omega S^\varepsilon_{tot}(x)\, dx}$$

of occupied sites to total sites is never more than

$$\frac{k_b \max_{x\in\Omega} M_0(x)}{k_d + k_b \max_{x\in\Omega} M_0(x)}. \tag{35}$$

4.2. Uniform estimates.

4.2.1. Invariant regions. In order to be able to take the limit of the solutions as $\varepsilon \to 0$, we need certain uniform bounds on those solutions. Some of the required bounds follow from the theory of invariant domains. See [24, Chap. 14] for an introduction and references. The version we will apply, in which the hypotheses have been weakened somewhat, is the following special case of [21, Thm. 3].

THEOREM 3. *Assume that the following hold:*

1. *Domain: Ω is either a smooth bounded domain or the exterior of a smooth bounded domain.*

2. *Smoothness:* $u := (u_1, \ldots, u_p)$ *is continuous on* $[0,T] \times \overline{\Omega}$, *and* u_t, u_{x_j}, *and* $u_{x_j x_k}$ *are continuous on* $(0,T) \times \Omega$.
3. *PDE:* u *satisfies the system*

$$\partial_t u_j - d_j \Delta u_j = f_j(t,x,u) \tag{36}$$

for $0 < t < T \leq \infty$ *and* $x \in \Omega$, *where* $d_j \geq 0$ *and* $f_j \in C^1$.
4. *Region: The region* $\mathcal{R} := \{u \mid a_j \leq u_j \leq b_j\}$ *is invariant for the system of ODEs obtained by setting every* d_j *in* (36) *to zero, i.e.,* $f_j \leq 0$ *when* $u_j = b_j$ *and* $a_k \leq u \leq b_k$ *for each* $k \neq j$, *and* $f_j \geq 0$ *when* $u_j = a_j$ *and* $a_k \leq u \leq b_k$ *for each* $k \neq j$.
5. *Initial condition:* $u(0,x) = u_0(x)$ *for* $x \in \Omega$, *where* $u_0(x) \in \mathcal{R}$ *for all such* x.
6. *Boundary condition:* $\partial_\nu u = 0$ *for* $0 < t < T$ *and* $x \in \partial\Omega$, *where* ν *denotes the exterior normal on the boundary* $\partial\Omega$.
7. *Behavior at infinity: If* Ω *is unbounded, then* $u(t,x) = o(|x|^2)$ *as* $x \to \infty$.

Then the solution $u(t,x)$ *remains in* $\mathcal{R}$ *for* $0 \leq t \leq T$ *and* $x \in \overline{\Omega}$.

The region that we wish to show to be invariant for (22)–(23) depends on x, as will be apparent below, so Theorem 3 does not apply directly. That theorem could be extended to the case of x-dependent invariant regions either by using the fact that the S-component does not diffuse or via the approach of [15]. However, it will in any case be convenient to transform our system via

$$N^\varepsilon = 1 + \frac{k_b M^\varepsilon}{k_d}, \qquad R^\varepsilon = \frac{S^\varepsilon}{S^\varepsilon_{\rm tot}(x)}, \tag{37}$$

which yields equations whose invariant sets will not depend on x. Although $S^\varepsilon_{\rm tot}(x)$ vanishes in much of the domain Ω, which makes $R^\varepsilon(0,x)$ undefined, the initial condition (28) implies that $R^\varepsilon(0,x) \equiv 1$ where $S^\varepsilon_{\rm tot}(x)$ is nonzero, so the initial data for R^ε extend naturally to

$$R^\varepsilon(0,x) = 1. \tag{38}$$

The initial data

$$N^\varepsilon(0,x) = 1 + \frac{k_b M_0(x)}{k_d} \tag{39}$$

for N^ε are obtained directly from those of M via the transformation (37).

In terms of the new variables N^ε and R^ε, system (22)–(23) becomes

$$N^\varepsilon_t = D\Delta N^\varepsilon + k_b S^\varepsilon_{\rm tot}(x)\left[1 - N^\varepsilon R^\varepsilon\right], \tag{40}$$

$$R^\varepsilon_t = k_d\left[1 - N^\varepsilon R^\varepsilon\right]. \tag{41}$$

The boundary condition (27) becomes

$$\nu \cdot \nabla N^\varepsilon = 0 \qquad \text{on } \partial\Omega. \tag{42}$$

LEMMA 4. *Suppose that* N^ε *and* R^ε *satisfy the system* (40)–(41) *plus the boundary condition* (42) *and have initial data* (38)–(39). *Define* $N_{\max} := \max N^\varepsilon(0,x)$. *Then*

$$1 \leq N^\varepsilon \leq N_{\max}, \qquad \tfrac{1}{N_{\max}} \leq R^\varepsilon \leq 1. \tag{43}$$

Proof. The vector field $(k_b S^\varepsilon_{\rm tot}(x)(1 - N^\varepsilon R^\varepsilon), k_d(1 - N^\varepsilon R^\varepsilon))$ points left and down at points above the curve $R^\varepsilon = \frac{1}{N^\varepsilon}$, and up and to the right below that curve. For

any k, that curve intersects the rectangle $1 \le N^\varepsilon \le k$, $\frac{1}{k} \le R^\varepsilon \le 1$ at the upper left and lower right corners, and so points inwards everywhere on the boundary of that rectangle, except at those corners, where it vanishes. Since $M_0(x) \ge 0$, the initial data (39) for N^ε satisfy $N^\varepsilon(0,x) \ge 1$, while the initial data for R^ε are identically one. Thus, the initial data lie in the rectangle (43). Now apply Theorem 3. ∎

Translating the bounds (43) back into the original variables $(M^\varepsilon, S^\varepsilon)$ yields Theorem 2.

In order to obtain convergence of solutions as $\varepsilon \to 0$ it is necessary to obtain estimates for derivatives as well. However, since $S^\varepsilon_{\rm tot}(x)$ and its derivatives are not uniformly bounded, it is not convenient to estimate the evolution of spatial derivatives of N^ε. But $S^\varepsilon_{\rm tot}(x)$ is independent of time, so we can obtain estimates for time derivatives; a spatial estimate will then be obtained by using the theory of elliptic PDEs.

LEMMA 5. *Let N^ε and R^ε satisfy the conditions of Lemma* 4. *Suppose in addition that condition* (30) *holds and that for some $\tilde b_\pm$,*

$$\tilde b_- \le D\Delta N_0(x) \le \tilde b_+. \tag{44}$$

Then for some b_-, b_+, B_-, and B_+

$$b_- \le N^\varepsilon_t \le b_+, \qquad B_- \le R^\varepsilon_t \le B_+. \tag{45}$$

Proof. Since the equation for R^ε is an ODE, a uniform bound on its time derivative follows from the bounds for N^ε and R^ε; i.e., the second half of (45) holds. Taking the time derivative of (40) for N^ε and substituting for the time derivative of R^ε from (41) yields

$$(N^\varepsilon_t)_t = D\Delta(N^\varepsilon_t) - k_b R^\varepsilon S^\varepsilon_{\rm tot}(x)\left[(N^\varepsilon_t) + \frac{k_d N^\varepsilon(1-N^\varepsilon R^\varepsilon)}{R^\varepsilon}\right]. \tag{46}$$

The bounds (43) imply both a lower bound $\hat b_-$ and an upper bound $\hat b_+$ for the expression $\frac{k_d N^\varepsilon(1-N^\varepsilon R^\varepsilon)}{R^\varepsilon}$ appearing in (46). Condition (30) implies that $N^\varepsilon_t(0,x) = D\Delta N^\varepsilon(0,x)$, so the bounds (44) imply the same bounds for $N^\varepsilon_t(0,x)$. Define $b_- := \min\{\hat b_-, \tilde b_-\}$ and $b_+ := \max\{\hat b_+, \tilde b_+\}$. Since differentiating (42) with respect to time shows that $\nu\cdot\nabla(N^\varepsilon_t)$ also vanishes on the boundary, another application of Theorem 3 shows that the first half of (45) holds. ∎

4.2.2. Elliptic estimate. Solving (40) for ΔN^ε yields

$$\Delta N^\varepsilon = \frac{N^\varepsilon_t - k_b S^\varepsilon_{\rm tot}(x)\,[1 - N^\varepsilon R^\varepsilon]}{D}. \tag{47}$$

Although the right side of (47) is not known to be uniformly bounded, it is a uniformly bounded function times the known expression $S^\varepsilon_{\rm tot}(x)$ plus a bounded function. This will allow us to obtain uniform estimates for N^ε and R^ε in an appropriate Hölder space, and also to determine the behavior of $\nu\cdot\nabla N^\varepsilon$ near the boundary.

DEFINITION 6. *Let Ω be a domain in $\mathbb{R}^d$, let $B_r(x_0)$ denote the ball of radius r centered at x_0, and suppose that $1 \le p \le \infty$. A measurable function f belongs to the Morrey space $\mathcal{M}^p(\Omega)$ if*

$$\|f\|_{\mathcal{M}^p} := \sup_{x_0\in\Omega}\sup_{r>0} \frac{\int_{B_r(x_0)\cap\Omega} |f(x)|\,dx}{r^{d(1-1/p)}} < \infty. \tag{48}$$

An easy calculation shows that $L^p(\Omega) \subset \mathcal{M}^p(\Omega)$ [9, sect. 7.9]. However, the reverse is not true. In particular, although $S^\varepsilon_{\rm tot}$ is uniformly bounded in L^p only for $p = 1$, its structural properties (24)–(26) ensure that $S^\varepsilon_{\rm tot}$, and hence also $g(x)S^\varepsilon_{\rm tot}$ for any bounded g, belong to $\mathcal{M}^d(\Omega)$.

LEMMA 7. *Suppose that S^ε_{tot} satisfies* (24)–(26) *and that $g^\varepsilon(x)$ is uniformly bounded. Then for some fixed constant c,*

$$\|g^\varepsilon(x)S^\varepsilon_{\rm tot}(x)\|_{\mathcal{M}^d} \le c. \tag{49}$$

Proof. Since g^ε is bounded it suffices to prove estimate (49) for $g^\varepsilon \equiv 1$. Since assumptions (24)–(26) imply that the total number of sites $\int_\Omega S^\varepsilon(x)\,dx$ is uniformly bounded, for any positive δ

$$\sup_{x_0\in\Omega}\sup_{r\ge\delta}\frac{\int_{B_r(x_0)}|S^\varepsilon_{\rm tot}(x)|\,dx}{r^{d(1-1/p)}}$$

is uniformly bounded. By picking δ small enough so that the map

$$(y,\tau)\mapsto y+\tau\nu(y) \tag{50}$$

is one to one $\partial_i\Omega\times[0,\delta]$ and satisfies $|[y_1+\tau_1\nu(y_1)]-[y_2+\tau_2\nu(y_2)]|\ge c|y_1-y_2|$ there for some fixed positive c, we obtain that the intersection of the support of $S^\varepsilon_{\rm tot}$ with any ball $B_r(x_0)$ of radius at most δ is contained in a set of the form $\{y+\tau\nu(y)\mid y\in \partial_i\Omega\cap B_{kr}(y_0),\ \tau\in[0,\delta]\}$. Assumption (26) implies that the integral of $S^\varepsilon_{\rm tot}$ over such a set is bounded by a constant times the volume of a ball of radius kr in dimension $d-1$, which is a constant times r^{d-1}. Combining this with the bound for $r\ge\delta$ yields (49). ∎

Although integration against the Green's function for the Laplacian does not map L^1 into C^0 since functions in L^1 can tend weakly to a delta function, it does map $\mathcal{M}^p$ for p sufficiently large into the space $C^{0,\alpha}$ of Hölder-continuous functions for some appropriate positive α. We begin with a general result.

LEMMA 8. *Suppose that $f\in\mathcal{M}^p$ with $p>1$. Then for $\mu>\frac{1}{p}$, $Tf(x):=\int_\Omega\frac{f(y)}{|x-y|^{d(1-\mu)}}\,dy$ belongs to $C^{0,\alpha}$ for $\alpha<\min\{1,d(\mu-\frac{1}{p})\}$, where d is the spatial dimension. Furthermore, the $C^{0,\alpha}$ seminorm of Tf is bounded by a constant times the $\mathcal{M}^p$ norm of f.*

Proof. By interpolating between the elementary inequalities

$$\left|\frac{1}{|x_1-y|^\beta}-\frac{1}{|x_2-y|^\beta}\right|\le\left[\frac{1}{|x_1-y|^\beta}+\frac{1}{|x_2-y|^\beta}\right]$$

and

$$\left|\frac{1}{|x_1-y|^\beta}-\frac{1}{|x_2-y|^\beta}\right|\le c|x_1-x_2|\left[\frac{1}{|x_1-y|^{\beta+1}}+\frac{1}{|x_2-y|^{\beta+1}}\right],$$

we obtain that for any $\gamma\in[0,1]$,

$$\left|\frac{1}{|x_1-y|^\beta}-\frac{1}{|x_2-y|^\beta}\right|\le c(\gamma)|x_1-x_2|^\gamma\left[\frac{1}{|x_1-y|^{\beta+\gamma}}+\frac{1}{|x_2-y|^{\beta+\gamma}}\right]. \tag{51}$$

Pick $\alpha\in(0,1)$ such that $\alpha<d(\mu-\frac{1}{p})$. Applying (51) with $\gamma=\alpha$ and $\beta=d(1-\mu)$ yields

$$|[Tf](x_1)-[Tf](x_2)|\le c(\alpha)|x_1-x_2|^\alpha\sum_{j=1}^2\int_\Omega\frac{1}{|x_j-y|^{d(1-\lceil\mu-\frac{\alpha}{d}\rceil)}}f(y)\,dy. \tag{52}$$

Since $\mu - \frac{\alpha}{d} > \frac{1}{p}$ by construction, the integrals on the right side of (52) are bounded by [9, Lem. 7.18]. ∎

Using Lemma 8 we can show that N^ε and R^ε are uniformly bounded in some Hölder space.

LEMMA 9. *Under the conditions of Lemma* 5*, for bounded times the solutions* N^ε *and* R^ε *are uniformly bounded in* $C^{0,\alpha}$ *for* $\alpha < 1$.

Proof. Let G be the Neumann Green's function for the Laplacian in Ω, so that for any f having mean zero, the solutions to $\Delta u = f$ in Ω, $\frac{\partial u}{\partial \nu} = 0$ on $\partial\Omega$, are $u(x) = \int_\Omega G(x,y) f(y)\, dy + c$. The singularity of G when $x = y$ is of the same order as the Newtonian potential, i.e., $\frac{1}{|x-y|^{d-2}}$, or $\log(|x-y|)$ when $d = 2$. Since the smooth part of G makes a smooth contribution to u, it suffices to show that $\int_\Omega \frac{1}{|x-y|^{d(1-\mu)}} \Delta N^\varepsilon(y)\, dy$ belongs to $C^{0,\alpha}$ for $\alpha < 1$, where $\mu = \frac{2}{d}$ for $d > 2$ and is arbitrarily close to one for $d = 2$.

Now any bounded function belongs to $\mathcal{M}^\infty$ and hence also to $\mathcal{M}^p$ for any $p < \infty$. Hence (47) plus the bounds for N^ε, R^ε, and N_t^ε and Lemma 7 implies that ΔN^ε belongs to $\mathcal{M}^d$.

Lemma 8 therefore shows that $\int_\Omega \frac{1}{|x-y|^{d(1-\mu)}} \Delta N^\varepsilon(y)\, dy$ belongs to $C^{0,\alpha}$ for $\alpha < d(\frac{2}{d} - \frac{1}{d}) = 1$, and that its $C^{0,\alpha}$ seminorm is uniformly bounded. ∎

4.3. Taking the limit. By Ascoli's theorem, the uniform bounds obtained in the previous subsection imply the convergence along subsequences as $\varepsilon \to 0$.

COROLLARY 10. *Under the conditions of Lemma* 5*, for every sequence of values of* ε *there is a subsequence for which* N^ε *and* R^ε *converge uniformly in* Ω *for bounded times. The limits* N *and* R *satisfy the same bounds* (43) *as* N^ε *and* R^ε.

We first consider the limit in terms of the variables (N, R).

LEMMA 11. *The limits* (N, R) *satisfy*

$$N_t = D\Delta N \tag{53}$$

in Ω,

$$\nu \cdot \nabla N = \frac{k_b S_{tot}^0(y)(1 - NR)}{D} \tag{54}$$

on the inner boundary $\partial_i\Omega$ *bounding the tumor region,* (42) *on the outer boundary* $\partial_o\Omega$*, and*

$$R_t = k_d(1 - NR) \tag{55}$$

in $\overline{\Omega}$*, including in particular, on the inner boundary* $\partial_i\Omega$*. The initial values of* N *and* R *are the same as for the original system.*

Proof. Taking the weak limit of the PDE (40) yields (53) within the domain Ω, since N_t^ε converges weakly to N_t and the reaction term tends to zero in every compact subset of Ω. Since R^ε satisfies an ODE, the convergence of N^ε and R^ε implies that the limits satisfy (55). Since the convergence of N^ε and R^ε is uniform in time as well as space, their limits have the same initial values.

Finally, in order to obtain (54), let Ω_δ denote the subset of Ω whose distance to the inner boundary $\partial_i\Omega$ is less than δ. For sufficiently small δ, $\Omega_\delta = \{y + \tau\nu \mid y \in \partial_i\Omega,\ 0 < \tau < \delta\}$. The boundary of Ω_δ is then the disjoint union of $\partial_i\Omega$, and the set $\partial_\delta\Omega$ of points in Ω whose distance to $\partial_i\Omega$ is exactly δ. Since (53) implies that N is smooth in Ω, the derivative $\frac{\partial N}{\partial \nu}$ of N with respect to the outer normal on $\partial_\delta\Omega$ is well defined. As before, let $y(x)$ denote the mapping sending $x = y + \tau\nu$ to y.

By Green's formula, for any smooth function ψ

$$\int_{\partial_\delta\Omega}\psi(y(x))\frac{\partial N^\varepsilon}{\partial\nu}=\int_{\Omega_\delta}\psi\Delta N^\varepsilon-N^\varepsilon\Delta\psi+\int_{\partial_\delta\Omega}N^\varepsilon\frac{\partial\psi(y(x))}{\partial\nu} \tag{56}$$

since both $\frac{\partial N^\varepsilon}{\partial\nu}$ and $\frac{\partial\psi(y(x))}{\partial\nu}$ vanish on $\partial_i\Omega$.

Since $\frac{\partial\psi(y(x))}{\partial\nu}$ vanishes on $\partial_i\Omega$, it is $O(\delta)$ on $\partial_\delta\Omega$. Also, since N^ε is uniformly bounded and the volume of Ω_δ is $O(\delta)$, $\int_{\Omega_\delta}N^\varepsilon\Delta\psi=O(\delta)$. Similarly, upon substituting (47) into (56), the term involving N_t^ε contributes $O(\delta)$. Hence

$$\int_{\partial_\delta\Omega}\psi(y(x))\frac{\partial N^\varepsilon}{\partial\nu}=-\int_{\Omega_\delta}\psi(y(x))\frac{k_bS_{\rm tot}^\varepsilon(x)\,[1-N^\varepsilon R^\varepsilon]}{D}+O(\delta). \tag{57}$$

Now take the limit as first $\varepsilon\to0$ and then $\delta\to0$. The left side of (57) tends to $\int_{\partial_i\Omega}\psi(y)\frac{\partial N}{\partial\nu}$. Since the term $O(\delta)$ on the right side is uniform in ε, it contributes nothing to the combined limit. Hence

$$\begin{aligned}\int_{\partial_i\Omega}\psi(y)\frac{\partial N}{\partial\nu}\,d\sigma(y)&=-\lim_{\delta\to0}\lim_{\varepsilon\to0}\int_{\Omega_\delta}\psi(y(x))\frac{k_bS_{\rm tot}^\varepsilon(x)\,[1-N^\varepsilon R^\varepsilon]}{D}\,dx\\&=-\lim_{\delta\to0}\lim_{\varepsilon\to0}\int_{\Omega_\varepsilon}\psi(y(x))\frac{k_bS_{\rm tot}^\varepsilon(x)\,[1-N^\varepsilon R^\varepsilon]}{D}\,dx\\&=-\lim_{\delta\to0}\lim_{\varepsilon\to0}\int_{\partial_i\Omega}\psi(y)\int_0^\varepsilon\frac{k_bS_{\rm tot}^\varepsilon(y+\tau\nu)\,[1-N^\varepsilon(y+\tau\nu)R^\varepsilon(y+\tau\nu)]}{D}\,d\tau\,d\sigma(y),\end{aligned} \tag{58}$$

where we have used the fact that the difference between dx and $d\tau\,d\sigma(y)$ tends to zero with the distance from the boundary. Since the total integral of $S_{\rm tot}^\varepsilon$ is uniformly bounded, and $N^\varepsilon R^\varepsilon$ converge uniformly, we may replace that expression in (58) with its limit NR. In addition, $N(y+\tau\nu)R(y+\tau\nu)=N(y)R(y)+o(1)$, so in fact

$$\begin{aligned}&\int_{\partial_i\Omega}\psi(y)\frac{\partial N}{\partial\nu}\,d\sigma(y)\\&\quad=-\int_{\partial_i\Omega}\psi(y)\frac{k_b\,[1-N(y)R(y)]}{D}\left[\lim_{\varepsilon\to0}\int_0^\varepsilon S_{\rm tot}^\varepsilon(y+\tau\nu)\,d\tau\right]d\sigma(y)\\&\quad=-\int_{\partial_i\Omega}\psi(y)\frac{k_b\,[1-N(y)R(y)]}{D}S_{\rm tot}^{\varepsilon,0}(y)\,d\sigma(y)\\&\quad=-\int_{\partial_i\Omega}\psi(y)\frac{k_b\,[1-N(y)R(y)]}{D}S_{\rm tot}^0(y)\,d\sigma(y)\end{aligned} \tag{59}$$

by assumption (26). Since ψ is an arbitrary smooth function, (59) implies (54). ∎

In order to obtain convergence of the full sequence $(N^\varepsilon,R^\varepsilon)$ without restricting to some subsequence, it suffices to show that the limit obtained along different subsequences is unique.

LEMMA 12. *A bounded solution of* (53) *in* Ω, (54) *and* (55) *on the inner boundary* $\partial_i\Omega$, *and* (42) *on the outer boundary, with given initial data, is unique.*

Proof. Suppose that (N_j,R_j), $j=1,2$, are solutions having the same initial data. Define $N:=N1-N_2$ and $R:=R_1-R_2$. Multiplying the difference of (53) for N_1 and N_2 by N, integrating over Ω, and adding the integral over $\partial_i\Omega$ of R times the

difference of (55) for R_1 and R_2 yields

$$\begin{aligned}(60)\qquad &\frac{d}{dt}\frac{1}{2}\left[\int_\Omega N^2\,dx+\int_{\partial_i\Omega}R^2\,d\sigma(y)\right]\\ &\qquad=-D\int_\Omega\nabla N^2-\int_{\partial_i\Omega}\left[\frac{k_bS^0(y)}{D}N+k_dR\right]\,[R_1N+N_2R]\,d\sigma(y).\end{aligned}$$

Since both R_1 and N_2 are bounded and strictly positive, the elementary inequality $-c_1x^2+c_2xy-c_3y^2\le c_4y^2$ allows us to reduce (60) to

$$\begin{aligned}(61)\qquad &\frac{d}{dt}\frac{1}{2}\left[\int_\Omega N^2\,dx+\int_{\partial_i\Omega}R^2\,d\sigma(y)\right]\le c\int_{\partial_i\Omega}R^2\,d\sigma(y)\\ &\qquad\le c\cdot\frac{1}{2}\left[\int_\Omega N^2\,dx+\int_{\partial_i\Omega}R^2\,d\sigma(y)\right].\end{aligned}$$

Since $N\equiv0$ and $R\equiv0$ initially, (61) shows that they remain zero for all time. ∎

We are finally ready to prove the main result in terms of the original variables M^ε and S^ε.

Proof of Theorem 1. Lemma 12 implies the convergence of N^ε and R^ε to N and R holds without restricting to a subsequence. Upon transforming back to the variable M, (53) becomes (31). In view of the uniform convergence of R^ε, (26) implies the convergence of (34) to $S^0_{\text{tot}}R$, so (54)–(55) yield (32)–(33). The convergence of the initial data is obtained similarly. ∎

5. Possible extensions. In this study we have aimed to give both heuristic and rigorous justifications for using the laws of chemical kinetics to describe binding and dissociation reactions that take place on surfaces. Our results were obtained, however, for a specific model involving a single reaction taking place on the boundary, with purely diffusive dynamics away from the boundary. Furthermore, a more realistic model of the fluorophore-antibody–based imaging studied here should also include advection effects to account for the continuous drainage of the interstitial fluid. Other chemical and biological systems involve more complicated interactions, possibly including several reactions on the boundary. To what extent can our methods be applied in these more general situations?

Since both our heuristic and rigorous analyses implicitly or explicitly require uniform bounds on reaction concentrations or ratios, our methods seem to require the presence of an invariant region for the reaction dynamics. Models of a variety of chemical and biological systems for which the existence of such regions have been deduced or assumed have been studied [14, 16, 17].

Additional restrictions must be placed on reactants that concentrate at the boundary surface. First, the reaction terms must be at most linear in those reactants. In terms of our heuristic analysis, this condition arises because the volumetric concentrations of those reactants tend to Dirac delta functions, which makes superlinear functions of those concentrations diverge to infinity even when considered in the sense of distributions. In our rigorous analysis linearity is needed in order for the second change of variables in (37) to be helpful.

That reaction terms be at most linear in "surface" reactants seems to be a necessary condition for our results to hold, rather than a technical limitation. The presence of a superlinear growth term would make the reaction blow up as the reactant concentrates at the boundary, while superlinear decay terms would make reactions disappear in the limit.

Our methods can accommodate advection terms involving the "volumetric" reactants that do not concentrate at the boundary (e.g., advection of markers). Note, however, that our analysis does not apply to models that allow for advection or even diffusion of the "surface" reactants. Indeed, such advection or diffusion terms would change the model substantially, since they would cause the "surface" reactants to leave the region near the boundary.

REFERENCES

[1] B. Alberts, D. Bray, J. Lewis, M. Raff, K. Roberts, and J. D. Watson, *Molecular Biology of the Cell*, 3rd ed., Garland Publishing, New York, 1994.

[2] D. A. Frank-Kamenetsky, *Diffusion and Heat Transfer in Chemical Kinetics*, Plenum, New York, 1969.

[3] G. Gannot, I. Gannot, A. Buchner, H. Vered, and Y. Keisari, *Increase in immune cell infiltration with progression of oral epithelium from hyperkeratosis to dysplasia and carcinoma*, British Journal of Cancer, 86 (2002), pp. 1444–1448.

[4] G. Gannot, A. Buchner, and Y. Keisari, *Interaction between the immune system and tongue squamous cell carcinoma induced by* 4*-nitroquinoline N-oxide in mice*, Oral Oncol., 40 (2004), pp. 287–297.

[5] I. Gannot, A. H. Gandjbakhche, G. Gannot, P. C. Fox, and R. F. Bonner, *Optical simulations experiments for development of a noninvasive technique for the diagnosis of diseased salivary glands in situ,* J. Med. Phy., 27 (1998), pp. 1139–1144.

[6] I. Gannot, G. Gannot, A. Garashi, A. Gandjbakhche, A. Buchner, and Y. Keisari, *Laser activated fluorescence measurements and morphological features—an in vivo study of clearance time of FITC tagged cell markers*, J. Biomed. Opt., 7 (2002), pp. 14–19.

[7] I. Gannot, A. Garashi, G. Gannot, V. Chernomordik, and A. Gandjbakhche, *Quantitative* 3*-D imaging of tumor labeled with exogenous specific fluorescence markers*, J. Appl. Opt., 42 (2003), pp. 3073–3080.

[8] I. Gannot, A. Garashi, V. Chernomordik, and A. Gandjbakhche, *Quantitative optical imaging of pharmacokinetics of specific fluorescent tumor markers through turbid media such as tissue*, Opt. Lett., 29 (2004), pp. 742–744.

[9] D. Gilbarg and N. S. Trudinger, *Elliptic Partial Differential Equations of Second Order*, Springer-Verlag, Berlin, 1977.

[10] J. Hale and G. Raugel, *Reaction-diffusion equation on thin domains*, J. Math. Pures Appl., 71 (1992), pp. 33–95.

[11] A. Hammer, *Modeling, Analysis, and Optimization of Fluorescenated Antibody Based Imaging*, M.Sc. thesis, Tel Aviv University, Tel Aviv, 2003.

[12] D. Jones, H. V. Kojouharov, D. Le, and H. Smith, *Bacterial wall attachment in a flow reactor*, SIAM J. Appl. Math,, 62 (2002), pp. 1728–1771.

[13] L. S. Jung, J. S. Shumaker-Parry, C. T. Campbell, S. S. Yee, and M. H. Gelb, *Quantification of tight binding to surface-immobilized phospholipid vesicles using surface plasmon resonance: Binding constant of phospholipase* $A(2)$, J. Amer. Chem. Soc., 122 (2000), pp. 4177–4184.

[14] I. C. Kim, *Singular limits of chematoxis-growth model*, Nonlinear Anal. Ser. A: Theory Methods, 466 (2001), pp. 817–834.

[15] H. J. Kuiper, *Invariant sets for nonlinear elliptic and parabolic systems*, SIAM J. Math. Anal., 11 (1980), pp. 1075–1103.

[16] J. S. McGough and K. L. Riley, *A priori bounds for reaction-diffusion systems arising in chemical and biological dynamics*, Appl. Math. Comput., 163 (2005), pp. 1–16.

[17] M. Mincheva and D. Siegel, *Stability of mass action reaction-diffusion systems*, Nonlinear Anal., 56 (2004), pp. 1105–1131.

[18] P. F. Morrison, P. M. Bungay, J. K. Hsiao, B. A. Ball, I. N. Mefford, and R. L. Dedrick, *Quantitative microdialysis: Analysis of transients and application to pharmacokinetics in brain*, J. Neurochem., 57 (1991), pp. 103–119.

[19] H. Nygren, *Kinetics of antibody binding to surface-immobilized antigen. Analysis of data and an empiric model*, Biophys. Chem., 52 (1994), pp. 45–50.

[20] M. Praxmarer, C. Sung, P. M. Bungay, and W. W. van Osdol, *Computational models of antibody-based tumor imaging and treatment protocols*, Ann. Biomed. Eng., 29 (2001), pp. 340–358.

[21] R. Redlinger, *Invariant sets for strongly coupled reaction-diffusion systems under general boundary conditions*, Arch. Rational Mech. Anal., 108 (1989), pp. 281–291.

[22] A. R. Goldsby, T. J. Kindt, J. Kuby, and B. A. Osborne, *Immunology*, 4th ed., W. H. Freeman, San Francisco, 1997.
[23] J. Rauch and J. Smoller, *Qualitative theory of the FitzHugh-Nagumo equations*, Adv. in Math., 27 (1978), pp. 12–44.
[24] J. Smoller, *Shock Waves and Reaction-Diffusion Equations*, Grundlehren Math. Wiss. 258, Springer, Berlin, 1983.
[25] W. Z. Wei, S. Ratner, A. M. Fulton, and G. H. Heppner, *Inflammatory infiltrates of experimental mammary cancers*, Biochim. Biophys. Acta, 865 (1986), pp. 13–26.